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PEDIATRIC MORTALITY IN AFRICA: *PLASMODIUM FALCIPARUM* MALARIA AS A CAUSE OR RISK?

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Abstract. The disability adjusted life year (DALY) approach of defining cause-specific health burdens is becoming the benchmark for international disease control prioritization. For malaria, this categorical approach may not fully capture its burden that includes chronic anemia, low birth weight, and enhancement of the severity of other childhood diseases. We investigated the extent to which malaria acts as a risk factor for all-cause mortality in African children less than five years of age from 1) ecologic associations between *Plasmodium falciparum* infection prevalence (PR) and under-five mortality, and 2) reductions in all-cause under-five mortality achieved in malaria intervention trials. Across 48 demographic surveillance studies, when adjusted for secular trends, PR more than doubled all-cause mortality ($P = 0.0001$). Trials of insecticide-treated mosquito nets generally found smaller population-attributable fractions of pediatric mortality to malaria infection, which may relate to their imperfect coverage and efficacy. In conclusion, the disability and death burden due to malaria in African children could be higher than that detectable from cause-specific DALY estimations.

INTRODUCTION

The disability adjusted life year (DALY) approach of defining disease-specific public health burdens is slowly becoming the benchmark against which the international community invests in global disease control.[1] The impressive body of work published by the World Health Organization (WHO) on the global burdens of disease consistently single out the African continent as a region deserving particular attention for future health investment. In 2001, an estimated 24.4% of the global burden of disease was borne by Africa, home to only 10.7% of the global population.[2] The greater part of the DALY for sub-Saharan Africa is driven by high mortality in early childhood from a handful of infectious diseases (diarrheal and respiratory diseases, measles, and malaria) and high mortality in young adults from infection with human immunodeficiency virus (HIV) and tuberculosis.[2] The DALY approach has led to a renewed effort to better define disease-specific mortality rates. This has been a particular challenge in the high mortality regions of the world where, ironically, the least comprehensive and reliable vital registration systems exist. Despite the paucity of data, pan-African extrapolations of specialized survey data on acute respiratory tract infections,[3] HIV,[4] and malaria[5] have been used to re-estimate the contribution made by these infectious diseases to the African mortality burden.

Malaria in 2001 was ranked the eighth highest contributor to the global DALY and second in Africa.[2] The malaria DALYs were largely estimated from the combined effects of *Plasmodium falciparum* infection as a direct cause of death and the much smaller contributions of short duration, self-limiting, or treated surviving mild morbid events, malaria-specific anemia, and neurologic disability following cerebral malaria.[6] The estimate derives from an assumption that each illness event or death can only be attributed to a single cause. The DALY model does not allow sufficiently for malaria as an indirect cause of broader morbid risks, anemia (unless linked to acute high-density parasitemia), low-birth weight, or growth retardation/undernutrition,[7] disease states that are consequential to infection and illness, e.g., adverse reactions to treatment, neurologic disabilities, or cognitive impairment,[8] or the role of malaria infection in enhancing severity of other comorbid infectious diseases through immune suppression or enhanced invasive capacities across compartments.[9]

The categorical approach to causes of illness and death by focusing only upon the direct consequences of malaria infection may lead to an under-estimation of the contribution of malaria to the complete envelop of disability and death in Africa. Rather than assume that malaria is a piece of the disease burden pie, malaria might also be seen as a risk factor for the size of that pie. This has certainly been a persuasive argument proposed by nutritional epidemiologists when considering the role of undernutrition as a risk to childhood mortality, rather than a focus on extreme clinical manifestations of malnutrition.[10] Recently, the Comparative Risk Assessment project of the WHO has adopted this approach to re-examine the DALY as part of a counterfactual analysis of groupings of broad risks ranging from indoor air pollution to blood pressure.[11] During the first iterations of this model, the single largest contribution to the DALY in Africa was undernutrition during pregnancy and childhood. However, such models are limited by the amount of empirical data on patterns of exposure and on how the groupings of risk factors interact in a biologically plausible manner. The distinct advantage of a risk model is that it allows public health practitioners a basis upon for defining the potential broad health impact of removing or reducing individual risk.

There is a need to re-assess the true extent of the malaria-specific DALY while simultaneously entertaining the notion that malaria is a risk factor for the all-cause DALY. In this report, we re-examine the risks posed by malaria infection against the mortality component of the African childhood DALY. We approach the estimation of malaria risk through an ecologic analysis, relating empirical measures of exposure (prevalence of malaria infection) and outcome (death) across the continent and comparing these associations with the impact on mortality found in recent intervention (efficacy) trials aimed at reducing malaria exposure (risks).

MATERIALS AND METHODS

Data searches. Information was drawn from the Burden of Malaria in Africa (BOMA) project established in 1998 to

obtain data on morbidity, disability, and mortality associated with *P. falciparum* infection among African populations.[5,12,13]

The search strategy included the use of electronic databases (Medline®; SilverPlatter International, Washington, DC; Embase®; Elsevier Science, London, United Kingdom; and Popline®; Johns Hopkins School of Hygiene and Public Health, Baltimore, MD) using keywords malaria, *Plasmodium falciparum*, mortality, child survival, demography, and Africa. Unpublished Ministry of Health and regional conference material were also reviewed where available at libraries and archives in Kenya, Uganda, Sudan, South Africa, and Oxford, United Kingdom. References of all publications were checked to identify potential new material missed through initial searches. Authors of published material were contacted if information on precise geographic location, age, duration of follow-up, or person-years of exposure to risk were unclear from the original reports.

Mortality reports were included in the analysis where these were defined during prospective continuous demographic surveillance (DSS) among childhood populations of known periods of exposure-to-risk and frequent household visits to establish fatal events.[14] The DSS data provide a precise estimate of annualized mortality risks from birth to the fifth birthday.[14] The spatial coverage of DSS data across Africa is considerably more limited than are estimations from retrospective birth histories analyzed against model life tables, which are derived routinely from national demographic and health surveys (DHS). However, DSS concerns circumscribed areas of definable malaria risk, allowing the exploration of patterns of disease and death burden in the context of malaria transmission dynamics, whereas DHS data encompasses wide geographic areas of markedly varying but usually unknown malaria infection risks. We have only included DSS studies reporting annual all-cause mortality risks per 1,000 children 0–4 years old. Where DSS had hosted community or household randomized intervention trials, only control communities or baseline data were included. Mortality rates have been described in a number of sites over different time periods since 1982 and these have been treated separately with separate corresponding estimates of the parasite prevalence or retention of the same parasite prevalence estimates over time, on the assumption that the parasite prevalence had remained unchanged.

Measures of infection risk. We have assumed that the prevalence of *P. falciparum* parasite infection in a given childhood population represents an estimate of the frequency of parasite challenge in that community. The parasite rate is a widely used marker of malaria endemicity[15] and crudely corresponds to the frequency and duration of parasite exposure, but does not provide a precise quantification of the number of new infections received by a child each year. The non-linear relationship between challenge and infection prevalence has long been recognized.[16] Given the long persistence of parasitemia after a single infection,[17] it might be expected that parasite prevalence would become an increasingly blunt instrument at higher levels of transmission. A more reliable measure of infection risk is the entomologic inoculation rate (EIR), the product of the human biting rate (the number of vectors biting an individual over a fixed period of time, usually expressed per year) and the sporozoite rate (the proportion of vectors with sporozoites in the salivary glands). However, these latter estimates of infection risk are rare across Africa[18] and the methods used in its measurement under field conditions vary between studies.[19] Despite methodologic and interpretation limitations of both infection prevalence and EIR, Beier and others[20] have reviewed coincidental measures of the parasite prevalence in childhood and standardized estimates of EIR. Their analysis showed that more than 70% of the variance in parasite prevalence could be explained by the logarithmic classification of the EIR, overall and when analyzed by east and west Africa or by ecologic zone.

Independent data searches were used to locate a time and location specific estimate of infection prevalence for the geographic areas covered by the mortality surveillance. Cross-sectional surveys of infection prevalence were included if at least 50 randomly selected children between 0 and 4 years of age or, if that was not available, between 0 and 15 years of age. Where multiple cross-sectional surveys were undertaken, the survey undertaken at the peak malaria season was selected. Where only a single survey was available, it was not possible to estimate seasonal changes in prevalence; however, these changes are likely to be minimal under most endemic situations given the persistence of single infections over time.[17] Data were identified primarily through the MARA/ARMA database[21] or through correspondence with authors of mortality studies.

Statistical analysis. Statistical analysis was performed using SAS version 6.12 (SAS Institute Inc., Cary, NC). Data were first described using medians and interquartile ranges (IQRs) in accordance with four broad risk categories of malaria prevalence ($< 25\%$, 25–49%, 50–74%, and $\geq 75\%$) congruent with logarithmic increases in the EIR.[12,20] To model the contiguous relationships between mortality and parasite prevalence rates, weighted least squares regression was applied. In addition to parasite prevalence, the model considered as a variable the square of parasite prevalence; this variable allowed for the possibility of saturating or even decreasing mortality risks at the highest levels of parasite prevalence. The model considered as an additional variable the location of the study site within Africa, which was stratified into the categories west Africa, east-central Africa, and southern plus northern Africa.

The model took into account the calendar period of the study (1980–1989 and 1990–2002) because previous analyses have demonstrated that under-five mortality and malaria-attributed mortality in African DSS changed significantly over this period.[13] Studies were weighted in proportion to their precision, i.e., inversely in proportion to their variance, assuming Poisson distributions.[22] The proportion of variation in mortality explained (R^2) by each variable in the model was calculated in a stepwise regression analysis using forward selection.

RESULTS

Evidence from ecologic analysis. A total of 52 spatial and/or temporally independent prospective descriptions of mortality among children 0–4 years old were identified. Four studies were excluded because it was not possible to identify a spatially congruent estimate of parasite prevalence (two studies in Ethiopia,[23,24] one study in Somalia,[25] and one study in Malawi[26]). The remaining 48 estimates were derived from prospective surveillance; however, two studies did not fulfill the strict definition of a DSS.[14] These studies were under-

taken as part of active surveillance of cohorts among settled, displaced persons in the Sudan,[27] or a stable population of children residing on tea-estate in Western Kenya.[28]

Twenty-three data points represented 10 sites where more than one temporally distinct report of mortality was available. Overall, 16 countries contributed mortality information, seven from west Africa (Senegal, The Gambia, Burkina Faso, Guinea-Bissau, Sierra Leone, Benin, and Ghana), three from southern Africa (South Africa, Mozambique, and Zambia), five from east Africa and the Great Lakes region (Kenya, Tanzania, Uganda, Burundi, and Democratic Republic of Congo) and Sudan. Combined, these studies represent a total of 1,100,458 child years of follow-up and 35,647 deaths between the age of 0 and 5 years (Table 1).

The unadjusted median mortality rate for areas represented by a low prevalence of infection in childhood (less than 25%) was 13.7 per 1,000 children 0–4 years old per year (n = 10, IQR = 8.5, 19.0). This increased dramatically to 35.0 (n =

TABLE 1

Demographic surveillance studies of all-cause under-five mortality and estimates of malaria parasite prevalence (PR)*

Study area	Mortality references	Dates	PYO	Deaths	Mortality rate per 1,000 under-five years	PR	PR references
Dikgale, South Africa	54	1995–1999	3,596	28	7.9	0	21
Eastern Sudan	27	1997	4,295	47	10.9	1	27
Hai district, Tanzania	55	1992–1995	74,494	1,233	16.6	4	21
Hai district, Tanzania	56	1995–1999	106,807	1,876	17.6	4	21
Agincourt, South Africa	57	1992–1995	30,600	216	7.1†	6‡	58
Agincourt, South Africa	59	1995–1999	41,983	275	6.6	6‡	58
Brookebond, Kenya	28	1997–1998	30,623	325	10.6	12	28
Mbarara, Uganda	60	1988–1989	4,320	104	24.1	18‡	64
Muranga, Kenya	62	1985–1988	11,952	251	21.0	24	63
Dar es Salaam, Tanzania	55	1992–1995	34,023	883	26.0	28	64
Dar es Salaam, Tanzania	65	1995–1999	49,109	1,239	25.2	28	58
Manhica, Mozambique	66	1998–1999	11,491	347	30.2	32	67
Gwembe Tonga, Zambia	68	1991–1995	3,648	187	51.3	35	J. Chilumba, unpublished data
Bandim II, Guinea-Bissau	69	1987–1990	2,753	135	49.0§	35‡	70
Bandim II, Guinea-Bissau	71	1995–1997	17,840	1,025	57.5	35‡	70
Katana, Democratic Republic of Congo	72	1986–1987	5,187	358	69.0	35	49
Farafenni, The Gambia	73	1982–1983	2,505	171	68.3	37	74
Farafenni, The Gambia	75	1995–1999	14,016	541	38.6	37	74
Mlomp, Senegal	76	1985–1989	3,585	88	19.5	25	76
Mlomp, Senegal	76	1990–1995	4,301	106	21.8	49	76
Mlomp, Senegal	77	1995–1999	4,001	77	19.2	46	76
Kilifi, Kenya	78	1991–1993	20,679	455	22.0	49	38
Nouna, Burkina Faso	79	1993–1995	14,405	518	36.0	49	80
Nouna, Burkina Faso	79	1996–1998	15,058	513	34.1	49	80
Niakar, Senegal	76	1984–1989	29,491	1,913	60.0	50	76
Niakar, Senegal	76	1990–1995	29,491	1,329	41.7	50	76
Niakar, Senegal	81	1995–1999	26,106	1,209	46.3	50	76
Morogoro, Tanzania	55	1992–1995	50,071	1,795	35.8	52	82
Morogoro, Tanzania	83	1995–1999	70,037	2,772	39.6	52	82
Kongondjan area, Burkina Faso	84	1982–1986	1,271	43	36.2	54	84
Farafenni, South Bank Hamlets, The Gambia	45, 85	1988–1990	3,130	150	47.9	55	45, 85
Rufiji, Tanzania	86	1999–1999	11,518	376	32.6	55	87
Bo, Sierra Leone	88 and G. Barnish, unpublished data	1990	776	35	45.1	59	89
Bwamanda, Democratic Republic of Congo	90	1989–1991	7,088	246	34.7	62	21
Farafenni, PHC, The Gambia	45, 85	1988–1989	2,263	146	64.5	66	45, 85
Kassena-Nankana, Ghana	91	1995–1999	95,507	3,886	39.9	70	92
Upper River, The Gambia	93	1989–1993	113,319	3,776	33.3	71	94
Nyanza Lac, Burundi	95	1990–1991	3,815	160	41.9	76	95
Bagamoyo and Yombo, Tanzania	96	1992–1994	5,850	192	32.8	82	97
Pahou, Benin¶	50	1989–1989	1,117.5	29	26.0	83	98
Asembo Bay, Kenya	37	1997–1999	18,099	1,084	59.9§	83	99
Oubritenga, Burkina Faso	100	1995–1998	83,245	3,458	41.5	85	101
Navrongo, Ghana	102	1990	1,065	35	32.8	87	51
Tanga, Tanzania	103	1992–1993	2,072	90	43.4	88	104
Kilombero, Tanzania	105	1996–1997	8,761	279	31.8	90	106
Bandafassi, Senegal	76	1984–1989	8,488	609	63.8	95	76
Bandafassi, Senegal	76	1990–1995	8,488	558	58.4	95	76
Bandafassi, Senegal	107	1995–1999	8,200	479	58.4	95	76

* PYO = person-years of observation; PHC = primary health care.

† Assumed to be 7.1 per 1,000 person-years based on the reported 216 deaths over (3 years × 60,000 all-age population × 17% of population under age five = 180,000 person-years), instead of the reported 75 per million person-years.

‡ Antedating the mortality data by more than five years, on the assumption that parasite prevalence was stable over this time period.

§ Neonatal deaths excluded.

¶ 0–35 months only.

14, IQR = 25.4, 50.7) and 39.9 (n = 13, IQR = 35.8, 46.3) per 1,000 children per year among populations exposed to childhood parasite prevalence risks of 25–49% and 50–74%, respectively. Thereafter, all-cause mortality increased only marginally among communities exposed to the highest prevalence of infection (≥ 75%) to 41.9 per 1,000 children per year (n = 11, IQR = 32.8, 58.4).

In the regression model (Table 2 and Figure 1), mortality increased significantly with parasite prevalence ($P = 0.0001$), but this effect leveled off at higher prevalence rates, as shown by a negative effect of the square of parasite prevalence ($P = 0.053$). Parasite prevalence overall explained 64% of the variation in all-cause under-five mortality among the DSS, whereas the time period explained an additional 4.1%. For any given parasite prevalence, mortality decreased by approximately 10 deaths per 1,000 under-five years between 1982 and 1989 and 1990 and 1999 ($P = 0.016$); this is consistent with trends found in the same countries in nation-wide DHS surveys.[29] When these variables were accounted for, no influence was found of the region of Africa. Between 1982 and 1989, predicted mortality increased from 31 per 1,000 under-five-years (parasite prevalence = 18%) to 55 per 1,000 under-five-years (parasite prevalence = 95%. Between 1990 and 1999, mortality increased from 8 to 44 per 1,000 under-five years over a range of parasite prevalences of 0–95%. In other words, removing the risk of infection might reduce by more than two-fold the under-five mortality in Africa (Figure 1).

Evidence from intervention trials. The ecologic analyses described earlier suggest that malaria infection increases all-cause under-five mortality in rural African DSS by at least two-fold over the range of parasite prevalence described. However, these associations may not be causal; they might merely reflect the association of both malaria infection risk and mortality with other underlying factors (such as poverty) that determine both. To examine alternative evidence of the magnitude of the causal relationship, this section deals with how under-five mortality responds to reductions in malaria infection risk during malaria-specific intervention trials.

The best available evidence on the mortality impact of malaria control comes from a set of recent ITN trials that all measured the impact on all-cause under-five mortality in a randomized design. Earlier studies using residual spraying also showed major effects on all-cause under-five mortality (more than the malaria-attributed fraction),[27,30–32] but their detailed analysis has, due to sometimes less rigorous designed or documentation, proven complicated.[9,33] The ITN trials mostly refrained from looking at malaria-attributed deaths due to the problems during community studies of using verbal autopsies, which lack precision in distinguishing malaria and other infectious, febrile causes of death.[34,35] Their focus on all-cause mortality provided the opportunity to examine how the impact of malaria infection might operate beyond the direct effects of life-threatening, acute malaria episodes to include indirect, consequential and comorbid effects.

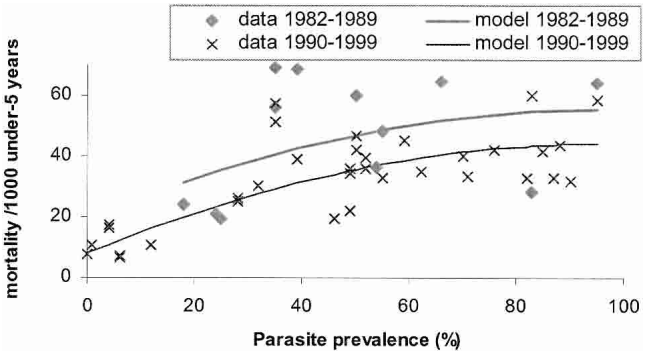

FIGURE 1. All-cause under-five mortality rates (per 1,000 under-five years) estimated by multivariate regression from 48 demographic surveillance studies in sub-Saharan Africa as a function of *Plasmodium falciparum* infection prevalence and calendar period. For regression statistics, see Table 2.

From the combined evidence of five trials settings,[36,37] it appears that in the short-term, reducing infection risk leads to an immediate impact in both high transmission and moderate transmission areas. On average, ITN usage averts approximately six deaths among children less than five years old, and this impact appears to be reasonably similar irrespective of the transmission intensity (or slightly higher in higher transmission sites; significance of trend; $P = 0.19$), as illustrated in Figure 2a. The proportional reduction in mortality tends to be higher in the low-transmission/lower-mortality sites ($P = 0.075$), since the same average six child lives saved constitute a larger proportion of a generally lower overall mortality rate (Figure 2b).[12,36,38,39]

Restricting the comparison to two trials undertaken in Kenya that resemble each other in terms of access to health care, similar health and drug policy, levels of drug resistance, and economic status allows a clearer understanding of the differences between protective efficacy and deaths averted. On the Kenyan coast, an area where children will receive between 1 and 10 new infections each year,[40] ITNs reduced the incidence of malaria infection among young children by 50%,[41] which resulted in a reduction in all-cause mortality among children 1–59 months old by 30% (95% confidence interval [CI] = 7–47%), or 3.8 lives per 1,000 child-years.[42] In an area of intense malaria transmission where children can expect to receive on average 60–300 infective bites per person per year[43] at Asembo Bay near Lake Victoria, ITNs reduced the incidence of new infections among young children by 74%.[44] The corresponding reduction in all-cause mortality among children 1–59 months old was higher than in Kilifi in terms of lives saved (8.0 lives per 1,000 child-years), but lower

TABLE 2

Weighted least-squares linear regression models describing the association between malaria parasite prevalence and all-cause under-five mortality (per 1,000 under-fives; 49 studies in Table 1)*

	Parameter estimate (SE)	*P*
Intercept	8.91 (2.868)	0.007
Plasmodium falciparum prevalence (%)	0.732 (0.166)	0.0001
Square of *P. falciparum* prevalence	–0.00370 (0.002)	0.053
Time period		
1982–1989	11.038 (4.455)	0.017
1990–2002	0 (reference category)	
Degrees of freedom in model	3	
R^2 (= proportion of explained variation)	0.681	

* Only the best fitting most parsimonious models, as determined by backward elimination of parameters not significant at the $P = 0.10$ level, are presented.

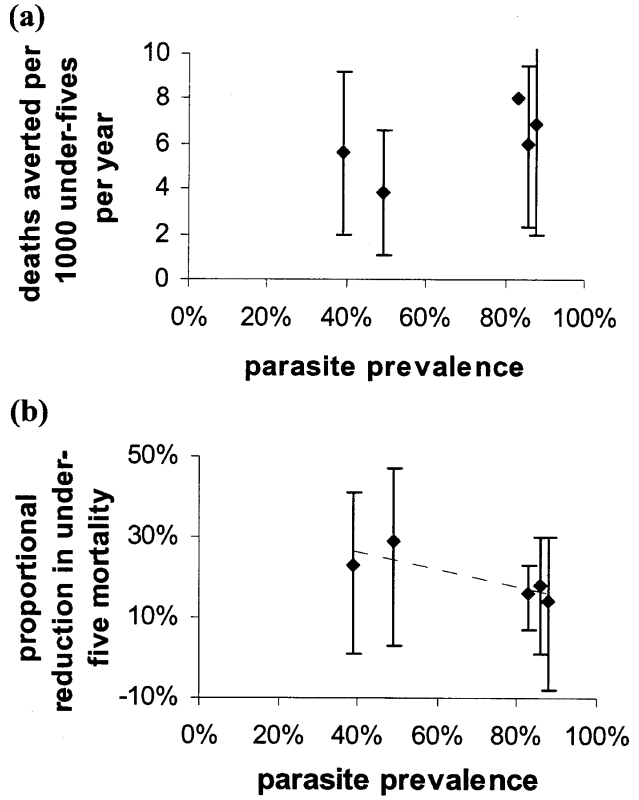

FIGURE 2. Relationship between under-five mortality reduction and background parasite prevalence (% of children less than five years of age) in African insecticide-treated net trials.[36,37] (**a**) Deaths averted per 1000 under-fives per year. (**b**) Proportional reduction in under-five mortality rate. Error bars represent the 95% confidence intervals around impact estimates. The dashed line in (**b**) represents the correlation between proportional mortality reduction and parasite prevalence ($R^2 = 0.70$, $P = 0.075$); for deaths averted, no relationship was found with parasite prevalence ($R^2 = 0.49$, $P = 0.19$). Parasite prevalences were estimated from Snow and others,[38] Blinka and others,[51] Greenwood and others,[74] Bloland and others,[99] and Habluetzel and others.[101]

than in Kilifi if expressed as a proportional reduction (16%, 95% CI = 6–25%, less child deaths).[37]

The observed average six under-five deaths saved per year among the ITN trials (Figure 2a) is less than the predicted >20/1,000 person-years decrease in under-five mortality associated with decreasing parasite prevalence (Figure 1). There are two possible explanations. First, the association may be overestimated due to ecologic confounding (both parasite prevalence and mortality may be determined by the same underlying factors, such as poverty, which inflates the apparent effect of parasite prevalence on mortality). Second, ITN use never completely eliminates the risks of malaria infection (due to limited efficacy and less than complete coverage), so their impact reflects less than the total of malaria-related mortality. For example, a trial combining ITN provision with weekly malaria chemoprophylaxis in The Gambia[45] demonstrated a reduction in all-cause mortality by almost two-thirds, indicating that the total impact of malaria may be larger than apparent from the trials focusing on ITN alone.

The comparative all-cause mortality results of trials of ITN under different malaria endemicities have been the subject of much comment.[12,38,39,46] The debate has focused on short versus long-term effects of reducing the frequency of parasite exposure and the development of functional immunity to the direct fatal consequence of malaria infection. Recent evidence from a high transmission area of northern Ghana suggests that early successes are retained over longer periods of observation.[47] The data presented from the ecologic comparisons continue to suggest saturation of mortality risks at the highest levels of parasite prevalence (Figure 1). However, our current understanding that the numbers of lives saved remains the same under all conditions of parasite prevalence (Figure 2a) supports starting efforts to implement ITN throughout Africa as a priority intervention to improve child survival.

DISCUSSION

In this review of available evidence, we have attempted to relate the risk of malaria infection with mortality in African populations less than five years old. Our model estimated that in rural DSS sites throughout sub-Saharan Africa, all-cause mortality increased by more than two-fold (25–30 deaths per 1,000 under-five years) over the range of prevalences of malaria infection. In regression analysis, parasite prevalence was the single most important risk factor that explained 64% of the variation between sites in all-cause under-five mortality. In comparison, during the global burden of disease estimations for 1990, malaria was labeled as the cause of only 14.6% of under-five deaths in sub-Saharan Africa,[6] and more recent iterations for the 2000 estimations malaria accounted for 20.2% of under-five deaths.[48] Both estimates relied upon DSS using verbal autopsy (VA) interviews about symptoms preceding deaths with bereaved relatives. These and other VA estimates[13] cover the ranges of mortality impacts provided during ITN trials (Figure 2); it is conceivable that the indirect malaria-related deaths missed by VA could be balanced by the less than 100% efficacy and coverage of ITN.

The health outcomes associated with risk factors from ecologic analyses must, however, be interpreted with caution. A main limitation of the current analysis is that we ignored the multiple possible confounders that might explain an ill-defined part of these associations. Notable among these influences would be socioeconomic variables, access to and effectiveness of health services, prevalence of HIV, exposure to other parasitic diseases, undernutrition, and the genetic make-up of the population. These variables were not available in a standardized format across the studies included in our analysis but we urge future epidemiologic studies and DSS collaborations, such as INDEPTH,[14] to collect these parameters for improved between-site, ecologic analysis. We anticipate that should additional risk factors be defined, the proportion of under-five mortality explained by the factors identified here would probably be less.

Nevertheless, the disability and death burden due to malaria is probably higher than that detectable from DALY models that regard malaria as a distinct clinical entity that can be measured reliably and fitted into a fixed disease-mix matrix. The true contribution of malaria infection to child mortality in Africa probably lies somewhere between the extremes of VA-defined causes of death and our ecologic analysis. Because there are discrepancies between direct malaria-attributed burden and associations between malaria infection

and pediatric health outcomes, descriptions of both risk and causation are both needed to defining malaria contribution to the public health burden. We would argue that neither approach alone provides a definitive answer; in combination they allow a range within which lies the contribution of the malaria parasites to morbidity and mortality. In practical terms, estimating categorical, single causes helps in priority setting. Alternatively, models that consider pathogens as a risk factors allow for a comprehensive public health framework to understand how targeted control might operate under different ecologic risk settings.

The African continent supports a huge variation in malaria infection risks ranging from less than one new infection per year to three new infections each day.[18] Recent derivations of malaria morbidity and mortality have attempted, in very crude terms, to stratify the continent in accordance with broad ranges of infection risk.[5] To truly exploit a risk tool for understanding interventions to reduce malaria burden requires an equally cogent series of high spatial resolution maps of malaria risk. Renewed efforts to map malaria risk in Africa began several years ago but to date there are only a few examples of national or sub-regional population-at-risk maps structured to reflect malaria infection prevalence shown on the x-axis of Figures 1 and 2.[52]

Causes of death and disability will always be something of an enigma. In the case of malaria, at a distal point in a continuum of causation the disease maintains populations in a constant state of poverty[53]; more proximally, pathology results in sequestered infection in the vasculature of the brain. The malaria parasite might exert both direct and indirect effects upon the DALY that are hard to capture through any single model. We would argue that malaria should be viewed as a cause of death and a risk factor for death to allow a more effective framework to prioritize, rationalize, and anticipate intervention impact.

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